Statens legemiddelverk

FHI Folkehelseinstituttet

MedNytt Metodevarsling for helsetjenesten

Metodevarsel

1. Status og oppsummering

Gene therapy for treatment of metachromatic leukodystrophy (MLD)

1.1 Oppsummering

Metoden omfatter et nytt virkestoff. Metoden har foreløpig ikke MT i Norge, EU eller i USA, men er under vurdering hos det Europeiske Legemiddelbyrået (EMA) og US Food and Drug Administration (FDA). Metoden er tilkjent orphan drug designation (legemiddel for en sjelden sykdom) (1).

1.2 Kort om metoden	1.3 Type metode	1.4 Finansieringsansvar	1.5 Fagfelt i MedNytt
ATC-kode: L Virkestoffnavn: *Autologous CD34+ cell enriched population that contains hematopoietic stem and progenitor cells transduced ex vivo using a lentiviral vector encoding the human arylsulfatase A gene.* Handelsnavn: Legemiddelform: *Autologous cells for infusion* MT-søker/innehaver: *Orchard Therapeutics*	☒ Legemiddel ☐ Diagnostikk ☐ Medisinsk utstyr ☒ Annet: Gene therapy	☒ Spesialisthelsetjenesten ☐ Folketrygd: blåresept ☐ Kommune ☐ Annet:	Neurology

1.6 Bestillingsanbefaling	1.7 Relevante vurderingselementer for en metodevurdering	
Metodevurderinger ☐ Fullstendig metodevurdering ☒ Hurtig metodevurdering (CUA) ☐ Forenklet vurdering ☐ Avvente bestilling ☐ Ingen metodevurdering Kommentar:	☒ Klinisk effekt relativ til komparator ☒ Sikkerhet relativ til komparator ☒ Kostnader / Ressursbruk ☒ Kostnadseffektivitet Kommentar:	☐ Juridiske konsekvenser ☐ Etiske vurderinger ☐ Organisatoriske konsekvenser ☐ Annet

2. Beskrivelse av metoden

Sykdomsbeskrivelse og pasientgrunnlag

MLD is a rare and fatal hereditary lysosomal storage disorder caused by changes (mutations) in the arylsulfatase A (ARSA) gene leading to deficiency of this enzyme in the body. The disease is characterized by accumulation of fats that causes the destruction of the protective fatty layer (myelin) surrounding the nerves in the brain and spinal cord. MLD is a progressive disease that is heterogeneous regarding the age of onset, disease progression and symptom severity. Symptoms vary by subtype but can include difficulty talking, seizures, difficulty walking, personality changes, behaviour and personality changes.

There are several forms of MLD, which are generally classified as Late-Infantile, Juvenile (sometimes subdivided into Early-Juvenile and Late-Juvenile) and adult MLD based on age at disease onset. In the late-infantile form, which is the most common form of MLD (50-60%), affected children begin having difficulty walking after the first year of life, usually at 15–24 months. Juvenile MLD has an onset between 3 and 10 years of age, usually beginning with impaired school performance. Adult -Onset MLD is the rarest form and commonly begins after age 16 years and, in the initial stages, is often mis-diagnosed as a psychiatric disorder because of personality changes.

Bone marrow or peripheral blood is collected from the patient, the haematopoietic stem and progenitor cells (CD34+ cells) are purified, modified with a lentiviral vector encoding the correct version of the ARSA gene (ARSA-LV) and cryopreserved (frozen). Once the patient has received conditioning medium (busulfan) the cells are thawed and returned to the patient via intravenous infusion. Only a single administration is envisaged where the dose given is according to body weight (range 3.0 - 30.0 x 10^6 CD34+ cells/kg). The objective is that the gene therapy leads to expression of normal or sufficient levels of ARSA to ameliorate (and potentially cure) the condition.

When both parents carry the same faulty gene, each pregnancy has a 25% chance of the child being affected. It is estimated that the UK incidence is approximately 1 in 40,000 (2). However, with modern diagnostic tools such as MRI Scans and genetic sequencing, it means that there are fewer incorrect diagnoses and it is possible that the incidence may prove to be higher.

Dagens behandling

Currently, there are no effective treatments for metachromatic leukodystrophy (MLD).
Drugs can be given to treat the symptoms as they occur, such as muscle spasms, infections, pain and seizures.

Virkningsmekanisme	This method (OTL-200) is a gene therapy that involves extraction of certain stem cells from a patient's bone marrow or blood. These stem cells are genetically modified and then returned to the patient by intravenous infusion to deliver the corrected version of the gene to the cells in charge of creating key proteins. The corrected cells then produce the protein that was missing or defective prior to treatment, aiming to halt disease progression or modify its natural course.
Tidligere godkjent indikasjon	None
Mulig indikasjon	Treatment of metachromatic leukodystrophy (MLD)
Kommentar fra FHI ved Companion Diagnostics [Dersom metoden dreier seg om companion diagnostics, skriver FHI om testen her]	☐ Metoden **vil medføre** bruk av ny diagnostisk metode (ny diagnostisk praksis) ☐ Metoden **vil ikke medføre** bruk av ny diagnostisk metode (allerede etablert diagnostisk praksis) Kommentar fra FHI:

3. Dokumentasjonsgrunnlag

3.1 Relevante og sentrale kliniske studier

Det foreligger klinisk dokumentasjon i form av minst en klinisk studie:

Populasjon (n=antall deltakere)	Intervensjon	Kontrollgruppe	Hovedutfallsmål	Studienummer, fase	Tidsperspektiv resultater
Male and female patients with MLD Infants 28 days – 3 months (n=6) Children 2-11 years (n=4) Total n=10.	OTL-200 Single infusion Follow-up for 8 years	None	Safety, efficacy, pharmacodynamics Open label, Non-randomised (single arm)	NCT03392987 205756 EudraCT: 2017-001730-26 Phase 3	Recruiting
Male and female patients with MLD 2-11 years (n=3) 12-17 years (n=3) Total n=6	OTL-200 Single infusion	None	Safety, efficacy, pharmacoynamics Open label, single arm, non-randomised	NCT04283227 OTL-200-07 EudraCT: 2019-002636-82 Phase 3	Recruiting
Male and females patients with early onset MLD < 7 years (n=20)	OTL-200 Single infusion	None	Safety and efficacy Open label, single arm, non-randomised	NCT01560182 201222 EudraCT: 2009-017349-77 Phase 1 / 2	Active, not recruiting Ad hoc data published (3)

3.2 Metodevurderinger og –varsel

Metodevurdering *- nasjonalt/lokalt -*	- Ingen relevante identifisert
Metodevurdering / systematiske oversikt *- internasjonalt -*	- Det foreligger minst en relevant internasjonal metodevurdering eller systematisk oversikt (4,5).
Metodevarsel	- Det foreligger minst et relevant metodevarsel (6,7).

4. Referanser

1. Orphan designation for autologous CD34+ cells transfected with lentiviral vector containing the human arylsulfatase A cDNA for the treatment of metachromatic leukodystrophy (2007) https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu307446
2. Great Ormond Street Hospital for Children NHS Foundation Trust. Available from: https://www.gosh.nhs.uk/conditions-and-treatments/conditions-we-treat/metachromatic-leukodystrophy-late-infantile-form [Accessed 13th May 2019].
3. Sessa M, et al. Lentiviral haematopoietic stem-cell gene therapy in early onset metachromatic leukodystrophy: an ad-hoc analysis of a no-randomised, open label, phase 1 / 2 trial. Lancet 2016; 388:476-87.
4. Ashrafi MR, et al. An update on clinical, pathological, diagnostic, and therapeutic perspectives of childhood leukodystrophies. Expert Rev Neurother. 2020;20(1):65-84.
5. OTL-200 for treating metachromatic leukodystrophy (ID1666) [nettdokument]. London: National Institute for Health and Care Excellence. Proposed (GID-HST10028). [oppdatert 6. april 2020; lest 23. april 2020]. Tilgjengelig fra: https://www.nice.org.uk/guidance/proposed/gid-hst10028/documents
6. Autologous lentiviral ARSA gene therapy [nettdokument]. Specialist Pharmacy Service, NHS. [oppdatert 7. januar 2020; lest 15. april 2020]. Tilgjengelig fra: https://www.sps.nhs.uk/medicines/arsa-gene-therapy/
7. OTL-200 for Metachromatic Leukodystrophy. Newcastle upon Tyne, UK: NIHR Innovation Observatory; 2019. Health Technology Briefing NIHRIO ID 23997.

5. Versjonslogg

5.1 Dato	5.2 Endringer gjort i dokument
22.05.2020	Laget metodevarsel
DD.MM.ÅÅÅÅ	Endret dokumentasjonsgrunnlag basert på nytt søk av DD.MM.ÅÅÅÅ
DD.MM.ÅÅÅÅ	Endret status for metoden